



Editorial: Recent advances in HBV and HCV immunology

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Viral hepatitis is a major public health problem. While a prophylactic vaccine is now available for hepatitis B virus (HBV), an estimated 240–350 million people worldwide are persistently infected with HBV (1–3). There is not yet an approved vaccine to prevent hepatitis C virus (HCV) infection, and between 130 and 200 million people are believed to be chronically infected worldwide (4–6). Untreated, HBV and HCV can each cause liver inflammation, fibrosis, and cirrhosis, and predispose patients to liver failure and hepatocellular carcinoma (2, 5). These infections are difficult and expensive to treat. Therapy for HBV infection may be life-long, and a true cure with loss of HBV cccDNA from the liver is rarely achieved (2). IFN α -based therapy was the only option for chronic HCV infection until recently; these regimens were often poorly tolerated and frequently ineffective. An array of direct-acting antiviral drugs has greatly improved the outlook for HCV therapy since 2011 (7), but the expense of the new drugs may limit the number of people who benefit. We still do not understand the immunologic mechanisms leading to chronic HBV and HCV infection, how the immune system controls these viruses, and how the immune system contributes to disease pathogenesis. These topics must be understood in order to develop improved therapies and, at least in the case of HCV, an effective vaccine. Our goal in this Research Topic is to cover advancements toward this understanding.

The immune response in the liver – where HBV and HCV each flourish – is incompletely understood. Many of our insights into the immune responses to HBV and HCV have come from studies of human peripheral blood, with limited comparisons to the cells in the liver. The liver is believed to constitute a tolerogenic environment as it receives portal venous blood rich in microbial products from the gut (8, 9). During persistent infection with either HCV or HBV, virus-specific T cells may decrease in number. The virus-specific T cells that can be found tend to have an exhausted phenotype including expression of inhibitory co-receptors, such as PD-1, CTLA-4, or Tim3 (10).

Age at the time of exposure is an important predictor of the outcome of HBV infection: those infected in the perinatal period or early in childhood are likely to experience chronic infection, while those infected as adults often mount a successful immune response, with elimination of the template cccDNA from the liver (2). Antiviral immune responses wax and wane during chronic HBV infection. In this Topic, Schuch and colleagues review the roles of CD8⁺ T cells and natural killer cells in HBV infection (11). Sharma and colleagues present a study of Treg cells in HBV-associated hepatocellular carcinoma (12). Rajoriya and colleagues review the roles of $\gamma\delta$ T cells in HBV or HCV infection as well as other conditions (13).

HCV causes persistent infection in an estimated 50–85% of those exposed (14). Innate and adaptive immune responses can drive spontaneous clearance of HCV infection. In this Topic, Abdel-Hakeem and Shoukry review the role of the immune response in resolution of HCV infection (15). Sung and colleagues focus on the roles played by CD8⁺ T cells during acute HCV (16). Genome-wide association studies have highlighted a role for IFN λ in determining the outcome of HCV infection and IFN α -based antiviral therapy; this issue is reviewed by Laidlaw and Dustin (17). Cashman and colleagues discuss the roles of humoral immunity in acute and persistent HCV

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infection (18). Chronic HCV infection is also associated with extrahepatic disease; Sidharthan and colleagues present gene expression study showing a role for monocytes in HCV-associated mixed cryoglobulinemic vasculitis (19). Because of shared modes of transmission, up to 30% of individuals with HIV infection may also be infected with HCV; co-infected individuals have increased inflammation and accelerated liver damage (14). Cho and colleagues present a study of T cell phenotype, activation, and

function in HCV–HIV co-infected patients, highlighting distinct changes in T cell function during co-infection – even when HIV is well controlled with highly active antiretroviral therapy (20).

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